NEW YORK HEART ASSOCIATION

Scientific Session on Research held at The New York Academy of Medicine
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PART I—ABSTRACTS OF PAPERS PRESENTED

*Action Potential Duration and Functional Refractory Period of Canine False Tendon, Papillary Muscle and Ventricular Epicardial Cells**

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In the case of premature extrasystoles and other dysrhythmias, the relationship of the Purkinje functional refractory period (FRP) to that of ventricular muscle assumes considerable importance in cardiac impulse conduction. *In vivo* experiments, using indirect recording methods, suggest that the canine Purkinje system has a shorter FRP than ventricular muscle. Opposite results have been reported *in vitro* using the intracellular recording technique. In an effort to clarify this apparent discrepancy, simultaneous intracellular recordings have been made from canine false tendons and papillary muscle during systematic variations in *in vitro* conditions. These *in vitro* studies have shown that alterations in the ionic composition of the perfusion fluid, substitution of blood or plasma for Tyrode's, the effect of time lapse following removal of the cardiac preparation from the animal, and addition of varying amounts of acetylcholine and/or epinephrine, do not change the *in vitro* relationship of the false tendon and papillary muscle FRP's and action potential durations (APD's). The only variable which was found to markedly influence this relationship was cycle length. At very short cycle lengths, produced by premature responses, the FRP and APD of false tendon and papillary muscle cells approached each other. In some experiments the FRP's of premature false tendon responses were less than corresponding papillary muscle values.

In another series of experiments the relationship between the APD's and FRP's of canine epicardial and endocardial cells was investigated. It was found that the epicardial cells had a shorter FRP and APD than endocardial units when studied at physiological rates. When simultaneous intracellular action potentials from epicardial and endocardial units were led into the two inputs of a differential amplifier, upright depolarization deflections ("QRS") with upright repolarization waves ("T waves") were observed. It is suggested that the difference in the FRP's and APD's of the epicardial and endocardial units may account for the direction of the T-wave in the electrocardiogram.

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*Lysine Uptake and Potassium Loss by Human Erythrocytes**

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A number of studies on hypokalemic alkalosis in animals suggests that basic amino acids, particularly lysine, may function as intracellular cations. As an approach to the investigation of the mode of transport of basic amino acids into cells, the uptake of lysine by human erythrocytes has been studied. Human erythrocytes suspended in plasma or in nonprotein media were incubated at 37°C. with radioactive lysine. Lysine entered the cells and potassium accumulated in the medium.

The following observations suggest that lysine enters erythrocytes by passive diffusion:

1) Blocking anaerobic glycolysis with iodoacetate did not interfere with lysine uptake.

2) The amount of lysine entering the cells was a constant fraction of the amount available, even at very high plasma lysine concentrations.

3) The uptake of lysine increased greatly as the pH of the medium was raised. Since the alpha amino group is not ionized at high pH it is suggested that the molecule diffuses more rapidly when it carries no net charge.

4) Comparison of uptake rates at 37°C and 4°C shows that the Q_{10} is about 1.8. Such a figure is suggestive of a passive process.

Analysis of the uptake rate at different pH levels indicates that lysine enters the cells at two different rates which seem to represent the rapid diffusion of the molecule with no net charge and the slower diffusion of the molecule with a net positive charge.

As lysine entered the cells, potassium accumulated in the medium. There did not appear to be any alteration in the transport of sodium and chloride.

Measurements were made of the extent to which lysine is bound to hemoglobin. On the basis of the figures for binding, the amount of free lysine inside the cells was calculated and found to be close to the amount of potassium accumulating in the medium.

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*Correlates of Renal Hemodynamics and Function in Hemorrhagic Shock in the Intact Dog: The Absence of Autoregulation of Renal Blood Flow and Glomerular Filtration Rate**

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While it is generally agreed that autoregulation of renal blood flow (RBF), i.e., constancy of RBF with alterations of blood pressure (B.P.), is absent following hemorrhage, such studies have been limited to the isolated kidney or to the *in situ* perfused kidney. Furthermore, since urine flow is not usually obtainable below 60 mm. Hg in the dog, there have been no studies on the intact animal which correlate changes of B.P. to glomerular filtration rate (GFR) and urine flow during hemorrhagic hypotension. Utilizing THAM, an amine buffer, and Mannitol, an osmotic diuretic, in order to obtain urine at low blood pressures, it was possible to derive information on the relationship of RBF, GFR, and urine flow to alterations of B.P. in the intact dog during shock.

Mongrel dogs were subjected to hemorrhagic shock for at least 20 minutes at B.P. 40-60 mm. Hg. Alterations of B.P. between 20 and 90 mm. Hg or higher were then accomplished by varying the height of the bleeding reservoir which was open and in continuity with the femoral artery. Infusions of THAM and Mannitol (8 ml./min.) were administered separately, either prior to or after shock. Mean B.P., urine flow, blood pH, and direct RBF were recorded. Creatinine clearances were obtained.

The results indicate complete absence of renal autoregulation of RBF and GFR following severe hemorrhagic shock in the intact dog. The pressure/flow and pressure/filtration curves tend to be linear or convex to the pressure axis. The pattern for urinary flow differs only slightly from that of glomerular filtration rate, as reflected by the relatively constant U:P ratios for creatinine. The findings are observed, both when the renal vascular resistance (RVR) is reduced following THAM, as when the RVR remains elevated as generally found in shock. It suggests, therefore, that the potential reactivity of the renal arterioles for dilation or constriction is not lost during shock, and that the state of vasomotor tone *per se* does not constitute the basis for the absence of the autoregulation mechanism. Furthermore, it favors the preglomerular arteriolar vasomotor localization for the simultaneous regulation of RBF and GFR.

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*Effects of Urea on Renal Concentrating Capacity in Man**

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The effects of exogenous urea on renal concentrating capacity were studied in moderately hydropenic subjects with low basal urine urea concentration (U_{ur}), in whom maximal ADH activity was ensured with vasopressin.

In six subjects the rate of solute-free water reabsorption, calculated as $T^c_{H_2O}$, was determined during urea diuresis from 2 to 7 ml./min. and compared with diuresis induced by a non-permeant solute (mannitol). For any given C_{osm}, T was approximately the same with mannitol and urea, providing U_{osm} had been similar in the prediuretic state.

In three subjects, in whom basal U_{ur} was varied with protein intake, repeated observations were made with small urea and mannitol loads. $T^c_{H_2O}$ increased with urea, as compared with mannitol, at urine flows below approximately 2 ml./min., whenever basal U_{ur} had been low. With steady diuresis over 2 ml./min., however, $T^c_{H_2O}$ did not increase, even if basal U_{ur} had been low. Enhancement of concentrating capacity was only observed when the reabsorbed fraction of the filtered load of urea was high (from 55 to 65 per cent, as determined from the C_{ur}/C_{cr} ratio).

These observations indicate that the role of urea in the concentrating operation in man depends on the rate of urine flow. At high V, the osmotic predominance of urea in the urine does not affect the rate of solute-free water reabsorption; at low V, however, urea may accumulate in the renal medulla and thereby increase the maximal osmotic pressure of the urine.

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*The Regulation of Coronary Blood Flow**

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The regulation of coronary blood flow has been investigated in open-chest anesthetized dogs. Cardiac effort was maintained at a steady level for extended periods while blood flow in a major coronary branch was subjected to sudden perturbations by imposition of sudden changes in coronary perfusion pressure. Different levels of stable cardiac effort were attained by transfusion, bleeding, or aortic constriction. A modification of perfusion techniques permitted determination of the instantaneous pressure-flow characteristics of the myocardial bed, i.e., for a particular level of vasomotor tone.

In each of over 400 observations in 14 dogs, a characteristic vasomotor response to pressure steps from control to perfusion pressures ranging from 20 to 240 mm. Hg. occurred. Abrupt changes in perfusion pressure caused abrupt changes in flow; within 0.5 seconds active coronary vasomotion intervened to return flow toward its normal level and stabilized flow within 8 to 30 seconds.

Poststabilization pressure-flow curves constructed from these pressure steps demonstrate:

1) complete compensation with independence of coronary flow from perfusion pressure over the range 70 to 145 (average) mm. Hg;

2) linear relationship between pressure and flow below 70 mm. Hg with critical closing pressures of 15 to 27 mm. Hg;

3) correlation between the level of regulated coronary flow and cardiac effort.

Instantaneous pressure-flow curves demonstrate steeper slopes and higher critical closing pressures as vasomotor tone increases.

The studies demonstrate an autoregulatory mechanism within the coronary bed which regulates coronary flow independent of perfusion pressure and in accordance with myocardial needs.

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*Primary and Secondary Pulmonary Vasopressor Responses to Acetylcholine Demonstrated by the Wedged Catheter Perfusion Technique**

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Pulmonary vasomotor responses to acetylcholine (ACH) have been suggested by studies of the excised perfused lung, and open-chest total lung perfusion. However, satisfactory separation of local from systemically induced responses has not been possible by these methods.

Controlled perfusion through a catheter properly wedged in a small pulmonary artery of the intact animal assures both constant flow and preservation of physiological reflexes, and permits description of a pressure-flow curve with precisely determined flows from 0.5 to 41 ml. per minute and simultaneously measured perfusion pressures. Perfusion with heparinized autogenous venous blood assures the metabolic integrity of the wedged segment. A microcatheter passed to the tip of the wedged catheter permits introduction of ACH directly into the pulmonary segment with a minimum period of contact with blood, and with precise timing of response.

ACH injected as a single bolus into the wedged segment results in a prompt rise in perfusion pressure. With a small dose, 0.5 to 1.0 gamma, this response is unattended by any detectable change in heart rate, left atrial, or systemic pressure. Choice of optimal perfusion rate allows selection of the most sensitive portion of the pressure-flow curve for demonstration of this vasomotor effect in the individual wedged segment. With a larger dose, 2.0 to 10 gamma, the rise in perfusion pressure precedes the systemic effects of ACH, and is differentiated temporally from the rise in perfusion pressure which occurs during the fall in systemic pressure.

A small dose of ACH given through a second catheter wedged in another segment produces no change in systemic pressure, and does not cause a pressure rise in the perfused wedged segment. However, a large dose of ACH through the second catheter will result in a fall in systemic pressure with bradycardia, without change in LA pressure, and with a concomitant rise in the perfused segment pressure. This late pressure rise in the perfused segment is clearly to be separated from the earlier primary response to ACH given directly into the perfused segment.

The "late" (20 second) pressure rise induced by ACH in the wedged pulmonary arterial segment can only be measured in a preparation in which constant flow is assured, a condition not met in previous intact animal studies. This effect of lowered systemic pressure on pulmonary vascular resistance can probably be explained by a carotid-sinus mediated baroreceptor reflex described by the Dalys in 1957.

The early pressure rise seen after local injection of ACH into the perfused wedged segment is independent of change in any other respiratory or circulatory parameter, and is conclusive evidence for a primary direct action of ACH in the pulmonary vascular bed.

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** Vincent Youman Memorial Research Fellow in Medicine.